DOI:
10.1016/j.drugalcdep.2018.11.008

Document Version
Peer reviewed version

Change in alcohol and other drug use during five years of continuous opioid substitution treatment

Brian Eastwood [1,2] *, John Strang [1], John Marsden [1,2]

[1] Addictions Department, Institute of Psychiatry, Psychology and Neuroscience,

King's College London, United Kingdom;

[2] Alcohol, Drug and Tobacco Division, Health Improvement Directorate,
Public Health England, United Kingdom

Author addresses:

Brian Eastwood
Programme Manager (Research and Outcomes), Evidence Application Team,
Alcohol, Drugs, Tobacco and Justice Division, Health Improvement Directorate,
Public Health England, 7th Floor Wellington House, 133-155 Waterloo Road, London SE1 8UG,
United Kingdom

John Strang
Professor of Addiction Psychiatry, King's College London,
Addictions Department, Box 48, Institute of Psychiatry, Psychology and Neuroscience,
DeCrespigny Park, Denmark Hill, London SE5 8AF, United Kingdom.
email: john.strang@kcl.ac.uk

John Marsden
Professor of Addiction Psychology, King's College London,
Addictions Department, Box 48, Institute of Psychiatry, Psychology and Neuroscience,
DeCrespigny Park, Denmark Hill, London SE5 8AF, United Kingdom.
email: john.marsden@kcl.ac.uk

Abstract: 250 words

Main text: 3,595 words

Tables: 5 in main text; 4 in on-line supplementary material

Figures: 2 in main text

---

* Corresponding author at: Alcohol, Drugs and Tobacco Division, Health and Wellbeing Directorate, Public Health England, 2nd Floor, Skipton House, 80 London Road, London SE1 6LH, United Kingdom.

E-mail address: Brian.Eastwood@phe.gov.uk

Abstract

Background: English national prospective, observational cohort study of patients continuously enrolled for five years in opioid substitution treatment (OST) with oral methadone and sublingual buprenorphine. This is a secondary outcome analysis of change in use of alcohol and other drug use (AOD) following identification of heroin use trajectories during OST.

Methods: All adults admitted to community OST in 2008/09 and enrolled to 2013/14 (n=7,717). Data from 11 sequential, six-monthly clinical reviews were used to identify heroin and AOD use trajectories by multi-level Latent Class Growth Analysis. OST outcome in the sixth and seventh year was ‘successful completion and no re-presentation’ (SCNR) to structured treatment and was assessed using multi-level logistic regression.

Results: With 'rapid decreasing' heroin use trajectory as referent, ‘continued high-level’ heroin use predicted ‘continued high-level’ crack cocaine use (relative risk ratio [RRR] 58.7; 95% confidence interval [CI] 34.2-100.5),‘continued high-level’ alcohol use (RRR 1.2; 95% CI 1.0-1.5), ‘increasing’ unspecified drug use (RRR 1.7; 95% CI 1.4-2.1) and less ‘high and increasing’ cannabis use (RRR 0.5; 95% CI 0.4-0.6). 'Increasing’ crack use was negatively associated with SCNR outcome for the ‘decreasing then increasing’ and 'gradual decreasing' heroin use groups (adjusted odds ratio [AOR] 0.5; 95% CI 0.3-0.9 and AOR 0.2; 95% CI 0.1-0.7, respectively).

Conclusions: Continued high-level heroin use non-response during long-term OST is associated with high-level crack cocaine and alcohol use, increasing unspecified drug use, but less high and increasing cannabis use. Increasing use of crack cocaine is negatively associated with the likelihood that long-term OST is completed successfully.

Keywords: Long-term, opioid substitution treatment; alcohol, cocaine, cannabis, trajectory

1. Introduction

Opioid substitution treatment (OST), with oral methadone or sublingual buprenorphine, is the first-line maintenance intervention for opioid use disorder (OUD). Observational studies have consistently reported OST to be associated with suppression of illicit opioid use (e.g. Hubbard et al., 2003; Mattick et al., 2014, 2009; Simpson et al., 1982; Teesson et al., 2006), a lower risk of opioid overdose (White et al., 2015), and reductions in crime (Russolillo et al., 2018).

Many people with OUD present for treatment with problems associated with several substance classes. Darke and Hall (1995) reported that 99% of heroin users had used another drug class in the six-months before treatment and reported using an average of 5.2 other substances. In England, national statistics demonstrate that crack cocaine is the most prevalent of concurrent substance use disorders and has increased in those starting treatment from 42% to 54% in the four years to 2017/18 (Public Health England [PHE], 2018a, 2017, 2016, 2015). Crack cocaine use during treatment for OUD is associated with poorer suppression of illicit opioid use, worse acquisitive crime and psychological health outcomes and a lowered likelihood of completing treatment successfully (Eastwood et al., 2017; Gossop et al., 2002a; Heidebrecht et al., 2018; Marsden et al., 2012, 2009). Concurrent alcohol use disorder has been reported to affect around a third of OUD patients in treatment, although in England the prevalence is somewhat lower at 17% (Nolan et al., 2016; Public Health England, 2018a).

There have been mixed findings from observational follow-up studies of change in concurrent alcohol and other drug use (AOD) during OUD treatment. Brecht et al. (2008) observed an aggregate reduction in use, while Gossop et al. (2003) reported a return to baseline levels following a temporary reduction, and others have reported a worsening state in a subset of non-users at treatment admission (Gossop et al., 2002b; Weiss et al., 2015). A two-year study of heroin users enrolled in the Australian Treatment Outcomes Study reported that reductions in heroin use were not associated with increases in the use of cocaine, amphetamine, cannabis, benzodiazepines and other opioids (Darke et al., 2006). A longer 11-year follow-up study reported the use of alcohol was to be consistent across waves, ranging between 49% and 56% (Darke et al., 2015). Similar reductions in alcohol and other drug use has been reported in Ireland over a 3-year follow-up period (Comiskey et al., 2009).

Aggregated findings may, however, mask differential clinical response among sub-populations. In their classic 30-year study of heroin and other drug use, Grella and Lovinger (2011) reported that a quarter of those followed up tracked a ‘rapid decrease’ heroin use trajectory and over half of these reported an early increase in AOD (although specific non-opioid substance classes were not reported). Recently, Teesson et al. (2017) identified six heroin use trajectory groups over 11-years. They reported that those following the ‘no decrease’ track were more likely to have been

incarcerated and to be currently affected by unstable housing and to be using benzodiazepines, but did not examine longitudinal patterns of concurrent substance use.

In a recent report in this journal, we identified five heroin use trajectories in a national cohort of patients who were continuously enrolled in OST for five years (n=7,719; Eastwood et al., 2018). We showed that patients following a positive treatment response trajectory towards abstinence were more likely to successfully complete treatment in the subsequent two-year period.

To inform clinical practice and treatment policy, studies are needed to determine specific substance use change trajectories during long-term OUD treatment. Accordingly, in this related article, we determined the strength of evidence:

(1) for a trajectory of patients characterised by increasing use of alcohol, cannabis, crack cocaine, cocaine powder, amphetamines and any unspecified drug use;

(2) that positive and negative change in heroin use is associated with an increase in alcohol and other drug use; and

(3) increased use of alcohol and other drug use predicts poor OST outcome.

2. Methods

2.1 Design

Using data from the English National Drug Treatment Monitoring System (NDTMS), this was a national, seven-year, prospective cohort study reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015). The study cohort has been described in two previous reports in the journal where a detailed description of measures is presented (Eastwood et al., 2018, 2017).

The present analysis concerns all patients who initiated OST between 1 April 2008 and 31 March 2009 and were enrolled for five years, ending 31 March 2014 and followed-up to 30 September 2016 (7,719 [14.2%] of 54,357). Following the NDTMS reporting protocol, all members of the cohort were either continuously enrolled in OST (i.e. they had a single unbroken episode of OST), or there was no more than 21 days between the end of one prescribing episode and the initiation of another (i.e. in the context of a transfer of a patient from one OST prescribing service to another).

2.2 Measures

2.2.1 Developmental trajectory indicators

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is a structured, clinical interview for substance use disorder treatment monitoring. Using a recall period of the past 28 days, the TOP is completed by the clinician at the patient's admission; then as part of a clinical review conducted

every six months, and at treatment completion. There were 11 TOP interviews conducted between Year 1 (2008/09) and Year 5 (2013/14) recording the number of days the patient reported using alcohol, cannabis, crack cocaine, cocaine powder, amphetamines, and any unspecified drug. The latter drug category is known only at the level of the treatment clinic. However, annual aggregate data suggest it is likely to involve benzodiazepines rather than anti-depressants, hallucinogens, volatile solvents, or major tranquillisers (10% prevalence versus <1%, respectively; Public Health England, 2018).

For the present analysis, we used the following five heroin use trajectory classes identified by Eastwood et al. (2018; **Figure 1**)[1]:

- Class 1 (n=1,617, 20.9%: '*gradual decreasing'*)
- Class 2 (n=1,672, 21.7%: '*decreasing then increasing'*)
- Class 3 (n=1,310, 17.0%: '*continued low-level'*)
- Class 4 (n=1,973, 25.6%: '*rapid decreasing'*)
- Class 5 (n=1,145, 14.9%: '*continued high-level'*)

2.2.2 Outcome measure

The OST outcome was the national summative measure of treatment effectiveness defined as successful completion and no re-presentation (SCNR) for further treatment within six months (Public Health England, 2018b). 'Successful completion' was recorded in Year 6 and Year 7 (ending 31 March 2016) by a clinician-verified report indicating: (1) abstinence from heroin (and any other non-medical opioids) and cocaine; (2) remission from OUD; (3) attainment of personal care plan goals and (4) completion of OST. For this summative measure of OST effectiveness, we removed all individuals to 30 September 2016 who were re-admitted to community-based or prison-based treatment, or were recorded on the Office for National Statistics' fatal drug-poisoning database.

2.2.3 Baseline covariate measures

Patient-level variables in the analysis included demographics (sex, age, ethnicity, employment, homelessness); social deprivation (linked to NDTMS based on the patient's residential postcode district or the location of their first treatment provider in instances of missing postcode information; Department for Communities and Local Government, 2007); treatment admission latent drug use class from Eastwood et al. (2017); drug injecting status; duration of heroin use 'career'; referral

[1] Due to the two individuals with no AOD data, the 'decreasing then increasing' and 'continued high-level' classes were each reduced by one individual for the present analysis.

route; other interventions (psychosocial; in-patient detoxification; or residential rehabilitation); and previous treatment for OUD.

2.3 Statistical analysis

Data management was done with SPSS (version 21). Given the clustering of patients within local treatment systems, we used multi-level Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping AOD use change trajectories across the five-years of OST (MPlus; version 7). Management of missing data (by multiple imputation) and all regression analyses was done with Stata (version 13).

2.3.1 AOD use trajectories

Sequentially, 1-class through 6-class models were fit to the data to identify unconditional trajectory membership. A Poisson distribution was assumed for all models and 5,000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). Trajectory identification was informed by the Aikaike and Bayesian information criteria, entropy and the Vuong-Lo-Mendel-Ruben and bootstrapped likelihood ratio tests. A minimum class size of 5% of the cohort was pre-specified for utility (Borders and Booth, 2012; Willey et al., 2016).

2.3.2 Missing data

As LCGA is implemented by full-information maximisation likelihood, all patients with at least one measurement could be assigned to a latent class, but a complete case sample may yield biased estimates due to missing covariate data. As such, and with no evidence that missing data was not missing-at-random, a set of twenty multiply imputed datasets was created using logistic regression, multinomial regression, and predictive mean matching for missing binary, multinomial or continuous data, respectively (Stata command: *MI impute chained*).

2.3.3 Analysis of heroin and AOD use trajectories

A series of multiply imputed, multivariable, multinomial logistic regressions regressed AOD use trajectory classes on heroin use trajectory groups, controlling for patient-level characteristics (Stata command: *mlogit*). Robust standard errors were utilised to calculate 95% confidence intervals (CI) to adjust for clustering of patients in each treatment system. Multiply imputed, multilevel, multivariable logistic regression models were used to estimate the likelihood of SCNR (Stata command: *meqrlogit*). As the likelihood of SCNR varied by heroin use trajectory, we estimated the association between AOD use trajectory groups and SCNR for each group.

3. Results

3.1 Study cohort

The study cohort includes 7,719 patients for which heroin use trajectories were identified (sample details in Eastwood et al. 2018). These patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23-71). Two patients did not complete a TOP assessment across all 11 assessment periods and were removed. Multilevel LCGA models were undertaken on 7,717 patients. A further 58 patients (0.8%) were subsequently removed as their original treatment records from 2008/09 were no longer available on NDTMS when assessing their follow-up status.

3.2 Heroin and AOD use during five years of continuous OST

Heroin use was reported by 85.8% of the cohort during the 28-days preceding treatment admission (**Table 1**). The most prevalent substances reported in the pre-admission month were alcohol (41.7%), crack cocaine (40.3%), cannabis (27.2%) and unspecified drugs (19.7%). Less than 5% reported using cocaine powder or an amphetamine.

At the end of Year 5, the prevalence of heroin use fell by almost half to 43.2%. The largest reduction in AOD use was observed for crack cocaine (20.6%), unspecified drugs (12.0%) and cannabis (6.7%). The prevalence of alcohol use was reduced by 2.7%. Although cocaine powder and amphetamines were reduced by 2.1% and 1.5%, respectively, this represented a reduction of over a third (36.6%) for amphetamines and nearly a half (44.7%) for cocaine powder. Due to the marginal prevalence of amphetamines and cocaine powder use in the cohort, these substances were not included in the models.

3.3 AOD use trajectories

Table 2 displays the results of the multilevel LCGA models for alcohol, crack cocaine, cannabis and unspecified drug. For each substance, AIC, BIC, aBIC, entropy and BLRT indicators all pointed to six-class solutions. However, based on the model indicators, as well as the longitudinal separation between trajectory groups, we judged that alcohol, crack cocaine, cannabis and unspecified drug were best described by a more parsimonious four, five, three and three class model, respectively.

Figure 2 (charts A-D) show the following trajectory classes:

Alcohol (**Figure 2A**: Class 1 [n=1,323, 17.1%: '*continued high-level*]; Class 2 [n=3,810, 49.4%: '*continued low-level*]; Class 3 [n=1,230,15.9%: 'increasing']; Class 4 [n=1,354, 17.6%: '*decreasing*']).

Crack cocaine (**Figure 2B**: Class 1 [n=735, 9.5%: '*gradual decreasing*']; Class 2 [n=924, 12.0%: '*increasing*']; Class 3 [n=4,576, 59.3%: '*continued low-level*']; Class 4 [n=407, 5.3%: '*continued high-level*']; Class 5 [n=1,075, 13.9%: '*rapid decreasing*']).

Cannabis (**Figure 2C**: Class 1 [n=4,565, 59.2%: '*continued low-level'*], Class 2 [n=1,834, 23.8%: '*low and decreasing*], Class 3 [n=1,318, 17.1%: '*high and increasing*'].

Unspecified drug use (**Figure 2D**: Class 1 [n=1,047, 13.6%: '*increasing*'], Class 2 [n=5,490, 71.1%: '*continued low-level'*], Class 3 [n=1,180, 15.3%: '*decreasing*'].

3.4 AOD trajectories regressed on heroin use

The distribution of AOD trajectory groups within each of the heroin use trajectory classes is shown in **Table 3.** Relative risk ratios (RRR) and 95% confidence intervals (CI) from the multiply imputed multivariable multinomial regression analyses of the relationship between heroin and AOD use are displayed in **Supplementary Tables 1-4**.

For brevity, we focused on the 'rapid decreasing' heroin class as the referent (Model 4, Supplementary Tables 1-4). Members of the 'continued high-level' heroin use class were:

- more likely to be members of the 'continued high-level' alcohol class (21.7% vs 15.5%: RRR 1.24; 95% CI 1.01-1.53), and less likely to be members of the 'decreasing' alcohol use class (12.1% vs 20.4%: RRR 0.57; 95% CI 0.45-0.71);
- more likely to members of crack cocaine 'continued high-level' (23.7% vs 0.8%; RRR 58.66; 95% CI 34.23-100.54), 'increasing' (17.3% vs 4.5%; RRR 6.45; 95% CI 4.89-8.51), 'gradual decreasing' (10.9% vs 3.4%; RRR 5.65; 95% CI 4.09-7.79) classes, were less likely to be members of the 'rapid decreasing' class (8.9% vs 22.3%; RRR 0.66; 95% CI 0.52-0.84);
- less likely to be members of the 'high and increasing' cannabis group (11.0% vs 19.2%: RRR 0.49; 95% CI 0.39-0.62); and
- more likely to be members of the 'increasing' unspecified drug class (17.6% vs 9.7%: RRR 1.70; 95% CI 1.36-2.12).

3.5 Probability of membership in the heroin use trajectory group

Table 4 shows the probability of membership in the heroin use trajectory group conditional on AOD classes. Among patients classified as members of 'decreasing' alcohol use trajectory, 10% were members of 'continued high-level' heroin non-response class, and 30% were members of the 'rapid decreasing' heroin good response class.

In the 'gradual decreasing' crack cocaine use class, 43% were members of the 'gradual decreasing' heroin use class, and among 'rapid decreasing' crack cocaine group, 41% were members of 'rapid decreasing' heroin use class. Only 1% of the 'continued high-level' crack cocaine use group were members of the 'continued low-level' heroin use class while 67% of this non-responding crack cocaine class were in the 'continued high-level' heroin use class. For cannabis, only 10% of the patients in the 'high and increasing' class up were members of the

'continued high-level' heroin use class. For the unspecified drug, only 14% of the continued low-level class were members of the 'continued high-level' heroin class and 27% were in the 'rapid decreasing' heroin group.

3.6 Treatment status at the end of Year 7

At the end of Year 7, 4,615 (60.3%) were still enrolled in OST. During Year 6 and 7, 1,986 (25.9%) exited treatment unsuccessfully, and 1,058 (13.8%) successfully completed treatment. Among this group, 16.5% (n=175) were re-admitted to treatment in the next six months, five were incarcerated and one person died from opioid-related poisoning. The SCNR outcome was therefore achieved by 877 of 3,044 patients discharged from OST (28.8%) .

SCNR was most likely to be attained by the 'rapid decreasing' heroin class (39.7%). The 'continued high-level' heroin use trajectory group was least likely to achieve the SCNR (16.2%), followed by the 'decreasing then increasing' group (19.6%). The 'continued low-level use' and 'gradual decreasing use' groups had similar levels of SCNR (31.2% and 31.7%, respectively).

3.7 Impact of AOD trajectory membership on outcome

Table 5 shows the results of the multiply imputed, multivariable, multilevel logistic regression analyses. Within the 'continued high-level' heroin use class, patients with a 'rapid decreasing' crack cocaine trajectory had an increased likelihood of achieving SCNR (adjusted odds ratio [AOR] 1.70; 95% confidence interval [CI] 1.04-2.77). Membership of the 'increasing' unspecified drug class was associated with a decreased likelihood of achieving SCNR (AOR 0.47; 95% CI 0.27-0.81).

Among the 'decreasing then increasing' heroin trajectory group, a decreased likelihood of achieving SCNR was associated with 'continued high-level' alcohol use (AOR 0.43; 95% CI 0.21-0.88), 'gradual decreasing' crack use (AOR 0.42; 95% CI 0.18-0.96), 'increasing' crack use (AOR 0.50; 95% CI 0.27-0.93) and 'low and decreasing' cannabis use (AOR 0.50; 95% CI 0.28-0.92).

There was a decreased likelihood of achieving SCNR for patients in the 'increasing' crack cocaine class within the 'gradual decreasing' heroin use class (AOR 0.22; 95% CI 0.07-0.66) and an increased likelihood of achieving SCNR for patients in the 'rapid decreasing' heroin class who were members of the 'low and decreasing' cannabis class (AOR 2.39; 95% CI 1.29-4.40).

4. Discussion

Over long-term continuous OST, we identified five trajectory classes for use of crack cocaine, four for alcohol, three for cannabis and three for unspecified drug use. In relation to our aims, each of these four substances contained an 'increasing' trajectory class. We found that the 'rapid decreasing' heroin trajectory group was less likely to be represented in both the 'increasing' crack cocaine and 'other drug' classes (although there was an increased likelihood of being represented

in the ‘high and increasing’ cannabis use group). Membership of the ‘increasing’ crack cocaine class was associated with a decreased likelihood of achieving the study outcome measure for two of the five heroin classes, while membership of the ‘increasing’ unspecified drug class was also associated with a decreased likelihood of achieving the outcome, at least for the ‘continued high-level’ heroin trajectory group.

4.1 Integration with the literature

Similar to other group based trajectory modelling studies (Grella and Lovinger, 2011; Teesson et al., 2017), we identified a sub-population of OUD patients who do not report a substantial improvement in drug use. In our study, we demonstrate that these patients are also more likely to use crack cocaine and alcohol at a higher frequency than other subpopulations, and the pattern of alcohol and other drug use has a detectable and negative influence on eventual successful completion of treatment. Grella and Lovinger (2011) reported that their ‘no decrease’ group was more likely to be represented in the ‘late-onset increase’ of alcohol and other drug use while Teesson et al (2017) noted that their ‘no decrease’ trajectory group were more likely to live in unstable accommodation, to be imprisoned and to have injection-related health problems. Taken together, this seems to indicate a subpopulation for whom multiple problems emerge across several domains.

The increased likelihood of ‘rapid decreasing’ and ‘continued low-level’ heroin trajectory groups being represented in the ‘high and increasing’ cannabis trajectory group may reflect the potential for use of cannabis to be associated with a pathway away from use of heroin during OST (Sifaneck and Kaplan, 1995). Daily cannabis use has also been associated with less severe heroin dependence, a lowered likelihood of daily heroin use and an increasing likelihood of never injecting heroin (Valdez et al., 2008). It is notable, however, that the increased use of cannabis in these two heroin groups did not confer any advantage in terms of completing OST successfully. If cannabis use does increase the likelihood of OUD recovery, it would be expected to be associated with treatment completion, though improved treatment outcomes have not been reported elsewhere (Budney et al., 2002; Epstein and Preston, 2003). While outside the scope of this paper, it is interesting to note the emerging evidence base of cannabinoid-opioid interactions within noradrenergic neural circuitry and the potential for cannabinoids to influence opioid withdrawal symptoms (Scavone et al., 2013).

4.2 Strengths and limitations

A key study strength is the national, large-scale follow-up of all individuals accessing treatment for opioid use disorder in England and the utilisation of the national outcomes monitoring system to measure change in heroin and concurrent substance use throughout patients’ long-term enrolment in treatment. This ‘concurrent recovery monitoring’ system (McLellan et al., 2005) is a powerful platform for policy makers and researchers to efficiently evaluate the effectiveness of community-

based treatment under routine conditions. In addition, unlike other comprehensive administrative databases (Sahker et al., 2015; Stahler et al., 2016), the consent model supporting NDTMS enables linkage with subsequent treatment admissions to provide a measure of sustained recovery from OUD in patients exiting the treatment system.

Several limitations are also acknowledged: first, while the frequency of use is captured by the Treatment Outcomes Profile, NDTMS does not capture the quantity of heroin and other drugs being consumed. It is possible that analysis of composite frequency by quantity metrics would yield different substance use trajectories, or that the 'continued high-level' groups do in fact demonstrate improvements in terms of quantity consumed. Second, NDTMS is a 'core dataset' and does not capture several covariates that may affect trajectory membership, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002c). Third, the observational design of this study does not allow inference of causality. It is not possible to determine whether low-level or reducing heroin use was caused by increased use of cannabis (or *vice versa*), or whether a complex set of causal factors are involved. Finally, it is unfortunate that illicit benzodiazepine use is not captured by the TOP. This remains an important clinical issue in the treatment of OUD and is reported by a sizeable minority in the English treatment system.

4.3 Clinical implications

Findings from this study and earlier reports underscore the challenge for OST services to support engagement and recovery for patients with illicit OUD. If OST does not supress a patient's heroin use to any clinically meaningful extent, then there is a likelihood that approximately 40% will use alcohol or crack cocaine at a consistently high or increasing level and 1 in 7 will report increasing use of other unspecified drugs. Helping a patient with heroin and poly-substance use may be very challenging, but this should be a high priority because of immediate health needs and because the success of OST is diminished. Screening for AOD use is recommended at treatment admission and at regular clinical reviews, which can be a rapid assessment (Ali et al., 2013), and the assessment of other important aspects of personal and social functioning should not be overlooked (Marsden et al., 2014).

If there is an unsatisfactory response to flexible dosing, it may be appropriate to suggest a change in medication (e.g. switching from methadone to buprenorphine), reinstate supervised administration (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017), or offer a targeted psychosocial intervention for opioids (Marsden et al., 2017), alcohol (Nolan et al., 2016) or cocaine (Marsden et al., 2018) from the service if there are resources or by referral. Although it may be discouraging that some patients continue to alcohol and other drugs, treatment may still offer provide important harm reduction benefits by reducing the risk of opioid poisoning (Cornish et al., 2010; White et al., 2015) and, taking a wider

societal perspective, there is an overall economic benefit-cost ratio from investing in OST (Zarkin et al., 2005).

4.4 Conclusions

This study highlights the importance of concurrent monitoring of adjunctive substance use in the treatment of opioid use disorder as a sizeable minority of patients either increase or maintain a high level of concurrent drug use and increasing drug use trajectories have a negative impact on positive outcome. These findings reinforce the conception of OUD as a complex and chronic condition. The next task for our research group is to examine the longitudinal inter-relationship between substance use, employment and housing.

Table 1. Heroin, alcohol and other drug use during five years of continuous OST (n=7,717)

	Treatment Outcomes Profile assessment										
Substance	Admission	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Heroin											
Responses (n)	5567	5774	6409	6449	6567	6649	6670	6712	6733	6742	6746
% using	85.8	62.7	59.2	57.0	53.3	43.6	39.6	40.6	41.9	42.6	43.2
Mean days using (SD) *	19.5 (11.6)	7.4 (9.7)	6.0 (8.7)	5.9 (8.6)	5.4 (8.3)	4.0 (7.5)	3.5 (6.9)	3.7 (7.1)	3.6 (7.0)	3.9 (7.2)	4.0 (7.4)
Alcohol											
Responses (n)	5496	5758	6407	6450	6569	6652	6675	6716	6737	6748	6739
% using	41.7	43.3	43.3	42.5	41.9	42.5	42.3	41.2	40.9	40.2	39.0
Mean days using (SD) *	5.4 (9.3)	5.2 (8.9)	5.3 (9.0)	5.2 (9.0)	5.3 (9)	5.3 (9.1)	5.5 (9.3)	5.3 (9.2)	5.4 (9.2)	5.3 (9.3)	5.3 (9.3)
Crack											
Responses (n)	5511	5761	6401	6444	6565	6642	6667	6708	6728	6738	6740
% using	40.3	25.1	20.4	20.3	20.3	19.6	19.2	19.2	19.1	19.2	19.7
Mean days using (SD) *	4.5 (8.5)	2.0 (5.4)	1.5 (4.4)	1.5 (4.5)	1.5 (4.7)	1.4 (4.5)	1.5 (4.6)	1.4 (4.3)	1.4 (4.3)	1.4 (4.4)	1.4 (4.5)
Cannabis											
Responses (n)	5463	5741	6391	6434	6555	6643	6670	6709	6721	6735	6731
% using	27.2	24.3	23.5	22.3	21.2	22.3	22.4	22.1	21.3	21.8	20.5
Mean days using (SD) *	3.8 (8.4)	3.5 (8.3)	3.5 (8.4)	3.4 (8.1)	3.2 (8.0)	3.4 (8.2)	3.5 (8.3)	3.5 (8.4)	3.4 (8.3)	3.5 (8.3)	3.2 (8.0)
Unspecified drug											
Responses (n)	5395	5684	6356	6407	6554	6627	6654	6695	6713	6710	6703
% using	19.7	9.5	8.3	7.3	7.4	6.9	7.1	7.3	7.2	7.9	7.7
Mean days using (SD) *	3.3 (8.1)	1.7 (6.3)	1.3 (5.6)	1.2 (5.4)	1.2 (5.2)	1.1 (5.0)	1.1 (4.9)	1.0 (4.9)	1.1 (5.0)	1.1 (5.0)	1.1 (5.1)
Cocaine powder											
Responses (n)	5438	5736	6391	6435	6559	6635	6655	6686	6700	6705	6701
% using	4.7	3.2	2.5	2.3	2.3	2.7	2.4	2.6	2.4	2.6	2.6
Mean days using (SD) *	0.2 (1.8)	0.1 (0.9)	0.1 (0.8)	0.1 (0.9)	0.1 (0.9)	0.1 (0.9)	0.1 (1.1)	0.1 (0.9)	0.1 (0.8)	0.1 (1.0)	0.1 (0.9)
Amphetamines											
Responses (n)	5434	5734	6390	6434	6559	6637	6660	6692	6700	6708	6705
% using	4.1	2.7	2.5	2.8	2.6	2.5	2.8	2.3	2.3	2.5	2.6
Mean days using (SD) *	0.4 (2.6)	0.1 (1.4)	0.2 (1.5)	0.2 (1.6)	0.2 (1.6)	0.2 (1.7)	0.2 (1.8)	0.2 (1.5)	0.2 (1.7)	0.2 (1.8)	0.2 (1.9)

SD = standard deviation

* Mean days of opioid use in past 28 days

Table 2 Unconditional multilevel latent class growth analysis of alcohol and other drug use over five years (n=7,717)

	Post-hoc criteria						Class proportion (probability of assignment)					
Substance	AIC	BIC	aBIC	Entropy	VLMR	BLRT	1	2	3	4	5	6
Alcohol												
Class 1	1035730.70	1035751.55	1035742.02	-	-	-	1.00 (1.00)					
Class 2	596761.37	596810.03	596787.78	0.994	<0.0001	<0.0001	0.67 (1.00)	0.33 (1.00)				
Class 3	518637.67	518714.13	518679.18	0.985	0.293	<0.0001	0.29 (0.99)	0.51 (1.00)	0.20 (0.99)			
Class 4	488513.21	488617.47	488569.81	0.980	0.135	<0.0001	0.17 (0.99)	0.49 (1.00)	0.16 (0.98)	0.18 (0.98)		
Class 5	466197.73	466329.81	466269.43	0.971	0.650	<0.0001	0.11 (0.97)	0.14 (0.99)	0.12 (0.98)	0.24 (0.97)	0.40 (0.99)	
Class 6	450851.39	451011.27	450938.18	0.967	0.200	<0.0001	0.12 (0.99)	0.11 (0.97)	0.15 (0.95)	0.09 (0.97)	0.14 (0.96)	0.40 (0.99)
Crack cocaine												
Class 1	521547.29	521568.15	521558.61	-	-	-	1.00 (1.00)					
Class 2	317093.91	317142.57	317120.33	0.988	<0.0001	<0.0001	0.27 (1.00)	0.73 (1.00)				
Class 3	272328.31	272404.78	272369.82	0.979	0.057	<0.0001	0.10 (0.99)	0.26 (0.98)	0.64 (1.00)			
Class 4	252515.88	252620.15	252572.48	0.974	<0.05	<0.0001	0.15 (0.96)	0.08 (0.99)	0.63 (1.00)	0.14 (0.97)		
Class 5	241212.70	241344.77	241284.40	0.965	0.210	<0.0001	0.10 (0.96)	0.12 (0.96)	0.59 (0.99)	0.05 (0.98)	0.14 (0.94)	
Class 6	233444.82	233604.70	233531.61	0.958	0.536	<0.0001	0.05 (0.98)	0.07 (0.96)	0.14 (0.93)	0.09 (0.90)	0.56 (0.99)	0.09 (0.97)
Cannabis												
Class 1	938291.53	938312.38	938302.85	-	-	-	1.00 (1.00)					
Class 2	535324.30	535372.95	535350.71	0.994	<0.0001	<0.0001	0.28 (1.00)	0.72 (1.00)				
Class 3	464870.58	464947.04	464912.09	0.988	0.319	<0.0001	0.59 (1.00)	0.24 (0.99)	0.17 (0.99)			
Class 4	432664.99	432769.26	432721.59	0.986	<0.05	<0.0001	0.13 (0.98)	0.14 (0.98)	0.60 (1.00)	0.13 (0.99)		
Class 5	412930.72	413062.79	413002.41	0.982	0.305	<0.0001	0.57 (1.00)	0.11 (0.98)	0.09 (0.99)	0.13 (0.97)	0.10 (0.98)	
Class 6	397768.05	397927.93	397854.84	0.983	0.103	<0.0001	0.56 (1.00)	0.07 (0.99)	0.08 (0.98)	0.11 (0.97)	0.11 (0.97)	0.08 (0.98)
Unspecified drug												
Class 1	539800.54	539821.40	539811.86	-	-	-	1.00 (1.00)					
Class 2	348344.25	348392.91	348370.66	0.991	<0.0001	<0.0001	0.27 (0.99)	0.73 (1.00)				
Class 3	297333.74	297410.20	297375.25	0.986	0.217	<0.0001	0.14 (0.99)	0.71 (1.00)	0.15 (0.98)			
Class 4	269356.09	269460.36	269412.70	0.985	0.623	<0.0001	0.69 (1.00)	0.07 (0.99)	0.10 (0.99)	0.14 (0.97)		
Class 5	246710.61	246842.68	246782.31	0.981	0.409	<0.0001	0.68 (1.00)	0.09 (0.98)	0.98 (0.96)	0.99 (0.99)	0.98 (0.98)	
Class 6	230945.90	231105.78	231032.69	0.980	0.0187	<0.0001	0.05 (0.99)	0.68 (1.00)	0.05 (0.99)	0.10 (0.95)	0.05 (0.97)	0.06 (0.97)

AIC: Akaike Information Criterion;
BIC: Bayesian Information Criterion;
aBIC: sample-size adjusted BIC;
VLMR: Vuong-Lo-Mendel-Ruben test;
BLRT: bootstrapped likelihood ratio test.

Table 3. Alcohol and other drug use trajectory group membership conditional on heroin use trajectory group

AOD use trajectory groups	Heroin use trajectory					Total (n=7,659)
	Gradual decreasing (n=1,604)	Decreasing then increasing (n=1,659)	Continued low-level (n=1,298)	Rapid decreasing (n=1,957)	Continued high-level (n=1,141)	
Alcohol						
Continued high-level	283 (17.6)	284 (17.1)	197 (15.2) [e]	304 (15.5) [e]	247 (21.7) [c,d]	1315 (17.2)
Continued low-level[+]	769 (47.9)	800 (48.2)	677 (52.2)	965 (49.3)	566 (49.6)	3777 (49.3)
Increasing	247 (15.4) [c]	312 (18.8) [c,d]	184 (14.2) [a,b,e]	288 (14.7) [b]	190 (16.7) [c]	1221 (15.9)
Decreasing	305 (19.0) [e]	263 (15.9) [d,e]	240 (18.5) [e]	400 (20.4) [b,e]	138 (12.1) [a,b,c,d]	1346 (17.6)
Crack cocaine						
Gradual decreasing	317 (19.8) [b,c,d,e]	197 (11.9) [a,c,d]	25 (1.9) [a,b,d,e]	67 (3.4) [a,b,c,e]	124 (10.9) [a,c,d]	730 (9.5)
Increasing	169 (10.5) [b,c,d,e]	368 (22.2) [a,c,d]	94 (7.2) [a,b,e]	87 (4.5) [a,b,e]	197 (17.3) [a,c,d]	915 (11.9)
Continued low-level[+]	793 (49.4)	837 (50.5)	1107 (85.3)	1352 (69.1)	448 (39.3)	4537 (59.2)
Continued high-level	51 (3.2) [c,d,e]	64 (3.9) [c,d,e]	5 (0.4) [a,b,e]	15 (0.8) [a,b,e]	270 (23.7) [a,b,c,d]	405 (5.3)
Rapid decreasing	274 (17.1) [b,c,e]	193 (11.6) [a,c,d]	67 (5.2) [a,b,d,e]	436 (22.3) [b,c,e]	102 (8.9) [a,c,d]	1072 (14.0)
Cannabis						
Continued low-level[+]	930 (58.0)	969 (58.4)	760 (58.6)	1133 (57.9)	737 (64.6)	4529 (59.1)
Low and decreasing	391 (24.4)	433 (26.1) [c,e]	271 (20.9) [b]	448 (22.9)	279 (24.5) [b]	1822 (23.8)
High and increasing	283 (17.6) [e]	257 (15.5) [c,e]	267 (20.6) [b,e]	376 (19.2) [b ,e]	125 (11.0) [a,b,c,d]	1308 (17.1)
Unspecified drug						
Increasing	245 (15.3) [c,d]	248 (15.0) [d]	159 (12.3) [a,e]	189 (9.7) [a,b,e]	201 (17.6) [c,d]	1042 (13.6)
Continued low[+]	1075 (67.0)	1189 (71.7)	934 (72.0)	1464 (74.8)	781 (68.5)	5443 (71.1)
Decreasing	284 (17.7) [b,e]	222 (13.4) [a]	205 (15.8)	304 (15.5)	159 (13.9) [a]	1174 (15.3)

Figures presented in table are number of participants (percentages)

[+] Represents the base outcome in the from all-case, multiply imputed, multivariable multinomial logistic regression models

[a,b,c,d,e] Represent significant statistical differences when different heroin use trajectory groups are used as referent categories (c.f. Supplementary Tables 1-4)

Table 4 Probability of heroin use trajectory group conditional on AOD use trajectory group

AOD use trajectory groups	Heroin use trajectory group					Total (n=7,659)
	Gradual decreasing (n=1,604)	Decreasing then increasing (n=1,659)	Continued low-level (n=1,298)	Rapid decreasing (n=1,957)	Continued high-level (n=1,141)	
Alcohol						
Continued high-level	283 (0.22)	284 (0.22)	197 (0.15)	304 (0.23)	247 (0.19)	1315 (1.00)
Continued low-level	769 (0.20)	800 (0.21)	677 (0.18)	965 (0.26)	566 (0.15)	3777 (1.00)
Increasing	247 (0.20)	312 (0.26)	184 (0.15)	288 (0.24)	190 (0.16)	1221 (1.00)
Decreasing	305 (0.23)	263 (0.20)	240 (0.18)	400 (0.30)	138 (0.10)	1346 (1.00)
Crack cocaine						
Gradual decreasing	317 (0.43)	197 (0.27)	25 (0.03)	67 (0.09)	124 (0.17)	730 (1.00)
Increasing	169 (0.18)	368 (0.40)	94 (0.10)	87 (0.10)	197 (0.22)	915 (1.00)
Continued low-level	793 (0.17)	837 (0.18)	1107 (0.24)	1352 (0.30)	448 (0.10)	4537 (1.00)
Continued high-level	51 (0.13)	64 (0.16)	5 (0.01)	15 (0.04)	270 (0.67)	405 (1.00)
Rapid decreasing	274 (0.26)	193 (0.18)	67 (0.06)	436 (0.41)	102 (0.10)	1072 (1.00)
Cannabis						
Continued low-level	930 (0.21)	969 (0.21)	760 (0.17)	1133 (0.25)	737 (0.16)	4529 (1.00)
Low and decreasing	391 (0.21)	433 (0.24)	271 (0.15)	448 (0.25)	279 (0.15)	1822 (1.00)
High and increasing	283 (0.22)	257 (0.20)	267 (0.20)	376 (0.29)	125 (0.10)	1308 (1.00)
Unspecified drug						
Increasing	245 (0.24)	248 (0.24)	159 (0.15)	189 (0.18)	201 (0.19)	1042 (1.00)
Continued low-level	1075 (0.20)	1189 (0.22)	934 (0.17)	1464 (0.27)	781 (0.14)	5443 (1.00)
Decreasing	284 (0.24)	222 (0.19)	205 (0.17)	304 (0.26)	159 (0.14)	1174 (1.00)

Table 5. Multiply imputed, multivariable, logistic regression models of SCNR outcome

AOD use trajectory groups	Heroin use trajectory				
	Continued high-level (n= 441; SCNR=16.2%)	Decreasing then increasing (n= 649; SCNR=19.6%)	Continued low-level (n= 504; SCNR=31.2%)	Gradual decreasing (n= 637; SCNR=31.7%)	Rapid decreasing (n= 813; SCNR=39.7%)
Alcohol					
Continued low-level	-	-	-	-	-
Continued high-level	0.47 (0.27,0.82)	**0.43 (0.21,0.88)**	0.66 (0.33,1.30)	0.75 (0.47,1.20)	1.29 (0.65,2.55)
Increasing	0.59 (0.34,1.01)	0.97 (0.53,1.76)	0.65 (0.34,1.23)	1.31 (0.82,2.08)	0.94 (0.43,2.08)
Decreasing	0.75 (0.46,1.22)	1.06 (0.57,1.97)	0.90 (0.51,1.59)	1.13 (0.76,1.69)	1.00 (0.42,2.39)
Crack cocaine					
Continued low-level	-	-	-	-	-
Gradual decreasing	0.98 (0.60,1.61)	**0.42 (0.18,0.96)**	0.22 (0.02,2.04)	0.49 (0.18,1.33)	1.15 (0.43,3.04)
Increasing	0.58 (0.29,1.16)	**0.50 (0.27,0.93)**	0.58 (0.23,1.44)	**0.22 (0.07,0.66)**	1.13 (0.53,2.41)
Continued high-level	1.18 (0.47,2.97)	0.86 (0.29,2.55)	- [a]	- [b]	1.23 (0.61,2.50)
Rapid decreasing	**1.70 (1.04,2.77)**	1.03 (0.54,1.97)	0.59 (0.20,1.77)	1.18 (0.81,1.71)	1.16 (0.41,3.30)
Cannabis					
Continued low-level	-	-	-	-	-
Low and decreasing	0.90 (0.57,1.43)	**0.50 (0.28,0.92)**	1.15 (0.68,1.95)	1.31 (0.90,1.90)	**2.39 (1.29,4.40)**
High and increasing	1.30 (0.80,2.12)	1.53 (0.84,2.76)	1.04 (0.59,1.83)	1.44 (0.96,2.17)	1.43 (0.59,3.42)
Unspecified drug					
Continued low-level	-	-	-	-	-
Increasing	**0.47 (0.27,0.81)**	1.04 (0.55,1.96)	0.70 (0.34,1.43)	0.88 (0.49,1.57)	0.97 (0.47,2.00)
Decreasing	0.84 (0.52,1.34)	1.28 (0.69,2.37)	1.02 (0.54,1.91)	0.70 (0.45,1.11)	0.92 (0.41,2.07)

Adjusted odds ratios for baseline covariates are not shown

[a] There were only 3 patients from the 'continued low-level' heroin trajectory group who were also in the 'continued high-level' crack cocaine trajectory, and these were removed from analysis.

[b] There were only 5 patients from the 'gradual decreasing' heroin trajectory group who were also in the 'continued high-level' crack cocaine trajectory, and these were removed from analysis.

Supplementary Table 1. Multiply imputed, multivariable, multinomial logistic regression models of alcohol trajectory group membership (n=7,717)

		Multinomial logistic regression model				
Alcohol trajectory group	Heroin trajectory group	Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Continued high level	Gradual decreasing	-	1.02 (0.84,1.25)	1.24 (1.00,1.54)	1.08 (0.89,1.31)	0.87 (0.70,1.07)
	Decreasing then increasing	0.98 (0.80,1.19)	-	1.21 (0.98,1.50)	1.05 (0.87,1.28)	0.85 (0.69,1.04)
	Continued low-level	0.81 (0.65,1.00)	0.82 (0.66,1.02)	-	0.87 (0.70,1.07)	**0.70 (0.56,0.88)**
	Rapid decreasing	0.93 (0.76,1.12)	0.95 (0.78,1.15)	1.15 (0.93,1.42)	-	**0.80 (0.65,0.99)**
	Continued high-level	1.15 (0.94,1.42)	1.18 (0.96,1.45)	**1.43 (1.14,1.80)**	**1.24 (1.01,1.53)**	-
Increasing	Gradual decreasing	-	0.84 (0.69,1.02)	**1.25 (1.00,1.56)**	1.05 (0.86,1.28)	0.97 (0.78,1.21)
	Decreasing then increasing	1.19 (0.98,1.44)	-	**1.48 (1.20,1.84)**	**1.25 (1.04,1.51)**	1.15 (0.93,1.42)
	Continued low-level	**0.80 (0.64,1.00)**	**0.67 (0.54,0.83)**	-	0.84 (0.68,1.04)	**0.78 (0.61,0.99)**
	Rapid decreasing	0.95 (0.78,1.16)	**0.80 (0.66,0.97)**	1.19 (0.96,1.47)	-	0.92 (0.74,1.14)
	Continued high-level	1.03 (0.83,1.28)	0.87 (0.70,1.07)	**1.29 (1.01,1.63)**	1.08 (0.87,1.34)	-
Decreasing	Gradual decreasing	-	1.21 (1.00,1.47)	1.09 (0.89,1.34)	0.92 (0.77,1.10)	**1.63 (1.29,2.05)**
	Decreasing then increasing	0.83 (0.68,1.00)	-	0.90 (0.73,1.11)	**0.76 (0.63,0.91)**	**1.35 (1.07,1.70)**
	Continued low-level	0.92 (0.75,1.12)	1.11 (0.90,1.36)	-	0.84 (0.70,1.02)	**1.49 (1.17,1.90)**
	Rapid decreasing	1.09 (0.91,1.30)	**1.31 (1.09,1.58)**	1.19 (0.98,1.44)	-	**1.77 (1.41,2.21)**
	Continued high-level	**0.61 (0.49,0.77)**	**0.74 (0.59,0.94)**	**0.67 (0.53,0.85)**	**0.57 (0.45,0.71)**	-

Relative risk ratios for baseline covariates are not shown

Supplementary Table 2. Multiply imputed, multivariable, multinomial logistic regression models of crack cocaine trajectory group membership (n=7,717)

		Multinomial logistic regression model				
Crack cocaine trajectory group	Heroin trajectory group	Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Gradual decreasing	Gradual decreasing	-	**1.65 (1.35,2.03)**	**18.59 (12.19,28.35)**	**8.10 (6.11,10.72)**	**1.43 (1.13,1.83)**
	Decreasing then increasing	**0.61 (0.49,0.74)**	-	**11.25 (7.32,17.29)**	**4.90 (3.65,6.57)**	0.87 (0.67,1.12)
	Continued low-level	**0.05 (0.04,0.08)**	**0.09 (0.06,0.14)**	-	**0.44 (0.27,0.70)**	**0.08 (0.05,0.12)**
	Rapid decreasing	**0.12 (0.09,0.16)**	**0.20 (0.15,0.27)**	**2.30 (1.44,3.67)**	-	**0.18 (0.13,0.24)**
	Continued high-level	**0.70 (0.55,0.89)**	1.15 (0.89,1.49)	**12.96 (8.27,20.33)**	**5.65 (4.09,7.79)**	-
Increasing	Gradual decreasing	-	**0.47 (0.38,0.58)**	**2.47 (1.88,3.24)**	**3.17 (2.41,4.16)**	**0.49 (0.39,0.62)**
	Decreasing then increasing	**2.11 (1.72,2.60)**	-	**5.21 (4.07,6.68)**	**6.69 (5.21,8.59)**	1.04 (0.84,1.28)
	Continued low-level	**0.41 (0.31,0.53)**	**0.19 (0.15,0.25)**	-	1.28 (0.95,1.74)	**0.20 (0.15,0.26)**
	Rapid decreasing	**0.32 (0.24,0.42)**	**0.15 (0.12,0.19)**	0.78 (0.57,1.06)	-	**0.16 (0.12,0.20)**
	Continued high-level	**2.04 (1.61,2.58)**	0.96 (0.78,1.19)	**5.02 (3.81,6.62)**	**6.45 (4.89,8.51)**	-
Continued high level	Gradual decreasing	-	0.80 (0.54,1.17)	**14.86 (5.88,37.58)**	**5.93 (3.30,10.66)**	**0.10 (0.07,0.14)**
	Decreasing then increasing	1.25 (0.85,1.84)	-	**18.63 (7.43,46.71)**	**7.43 (4.19,13.18)**	**0.13 (0.09,0.17)**
	Continued low-level	**0.07 (0.03,0.17)**	**0.05 (0.02,0.13)**	-	0.40 (0.14,1.10)	**0.01 (0.00,0.02)**
	Rapid decreasing	**0.17 (0.09,0.30)**	**0.13 (0.08,0.24)**	2.51 (0.91,6.95)	-	**0.02 (0.01,0.03)**
	Continued high-level	**9.9 (7.14,13.73)**	**7.89 (5.82,10.7)**	**147.10 (59.89,361.27)**	**58.66 (34.23,100.54)**	-
Rapid decreasing	Gradual decreasing	-	**1.47 (1.19,1.82)**	**5.60 (4.20,7.45)**	1.02 (0.85,1.22)	**1.55 (1.20,2.00)**
	Decreasing then increasing	**0.68 (0.55,0.84)**	-	**3.80 (2.83,5.11)**	**0.69 (0.57,0.84)**	1.05 (0.80,1.37)
	Continued low-level	**0.18 (0.13,0.24)**	**0.26 (0.20,0.35)**	-	**0.18 (0.14,0.24)**	**0.28 (0.20,0.39)**
	Rapid decreasing	0.98 (0.82,1.17)	**1.44 (1.19,1.75)**	**5.49 (4.18,7.21)**	-	**1.52 (1.19,1.94)**
	Continued high-level	**0.65 (0.50,0.84)**	0.95 (0.73,1.24)	**3.62 (2.60,5.05)**	**0.66 (0.52,0.84)**	-

Relative risk ratios for baseline covariates are not shown

Supplementary Table 3. Multiply imputed, multivariable, multinomial logistic regression models of cannabis trajectory group membership (n=7,717)

Cannabis trajectory group	Heroin trajectory group	Multinomial logistic regression model				
		Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Low and decreasing	Gradual decreasing	-	0.94 (0.79,1.10)	1.13 (0.94,1.36)	1.00 (0.85,1.17)	1.15 (0.96,1.38)
	Decreasing then increasing	1.07 (0.91,1.26)	-	**1.21 (1.01,1.45)**	1.07 (0.91,1.25)	**1.23 (1.03,1.47)**
	Continued low-level	0.88 (0.73,1.06)	**0.83 (0.69,0.99)**	-	0.88 (0.74,1.05)	1.02 (0.83,1.24)
	Rapid decreasing	1.00 (0.85,1.18)	0.94 (0.80,1.10)	1.14 (0.95,1.36)	-	1.15 (0.96,1.38)
	Continued high-level	0.87 (0.72,1.04)	**0.81 (0.68,0.97)**	0.98 (0.80,1.20)	0.87 (0.72,1.04)	-
High and increasing	Gradual decreasing	-	1.17 (0.96,1.42)	0.90 (0.74,1.10)	0.88 (0.73,1.05)	**1.79 (1.42,2.26)**
	Decreasing then increasing	0.86 (0.70,1.04)	-	**0.77 (0.63,0.94)**	**0.75 (0.63,0.90)**	**1.53 (1.21,1.94)**
	Continued low-level	1.11 (0.91,1.36)	**1.30 (1.06,1.59)**	-	0.98 (0.81,1.18)	**1.99 (1.56,2.54)**
	Rapid decreasing	1.14 (0.95,1.36)	**1.33 (1.11,1.60)**	1.02 (0.85,1.23)	-	**2.04 (1.62,2.56)**
	Continued high-level	**0.56 (0.44,0.71)**	**0.65 (0.52,0.83)**	**0.50 (0.39,0.64)**	**0.49 (0.39,0.62)**	-

Relative risk ratios for baseline covariates are not shown

Supplementary Table 4. Multiply imputed, multivariable, multinomial logistic regression models of other drug trajectory group membership (n=7,717)

Other drug trajectory group	Heroin trajectory group	Multinomial logistic regression model: Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Increasing	Gradual decreasing	-	1.06 (0.87,1.29)	**1.27 (1.01,1.59)**	**1.58 (1.28,1.94)**	0.93 (0.75,1.15)
	Decreasing then increasing	0.94 (0.78,1.15)	-	1.20 (0.96,1.49)	**1.49 (1.21,1.83)**	0.88 (0.71,1.08)
	Continued low-level	**0.79 (0.63,0.99)**	0.84 (0.67,1.04)	-	1.24 (0.99,1.57)	**0.73 (0.58,0.93)**
	Rapid decreasing	**0.63 (0.51,0.78)**	**0.67 (0.55,0.82)**	0.80 (0.64,1.01)	-	**0.59 (0.47,0.73)**
	Continued high-level	1.08 (0.87,1.33)	1.14 (0.93,1.41)	**1.37 (1.08,1.73)**	**1.70 (1.36,2.12)**	-
Decreasing	Gradual decreasing	-	**1.39 (1.15,1.69)**	1.18 (0.96,1.45)	1.19 (0.99,1.43)	**1.33 (1.07,1.65)**
	Decreasing then increasing	**0.72 (0.59,0.87)**	-	0.85 (0.68,1.05)	0.86 (0.71,1.04)	0.95 (0.76,1.19)
	Continued low-level	0.85 (0.69,1.04)	1.18 (0.95,1.46)	-	1.01 (0.83,1.24)	1.13 (0.89,1.42)
	Rapid decreasing	0.84 (0.70,1.01)	1.17 (0.96,1.41)	0.99 (0.81,1.21)	-	1.11 (0.90,1.38)
	Continued high-level	**0.75 (0.61,0.94)**	1.05 (0.84,1.31)	0.89 (0.70,1.12)	0.90 (0.73,1.11)	-

Relative risk ratios for baseline covariates are not shown

Figure 1. Heroin use trajectories over 5 years of continuous OST

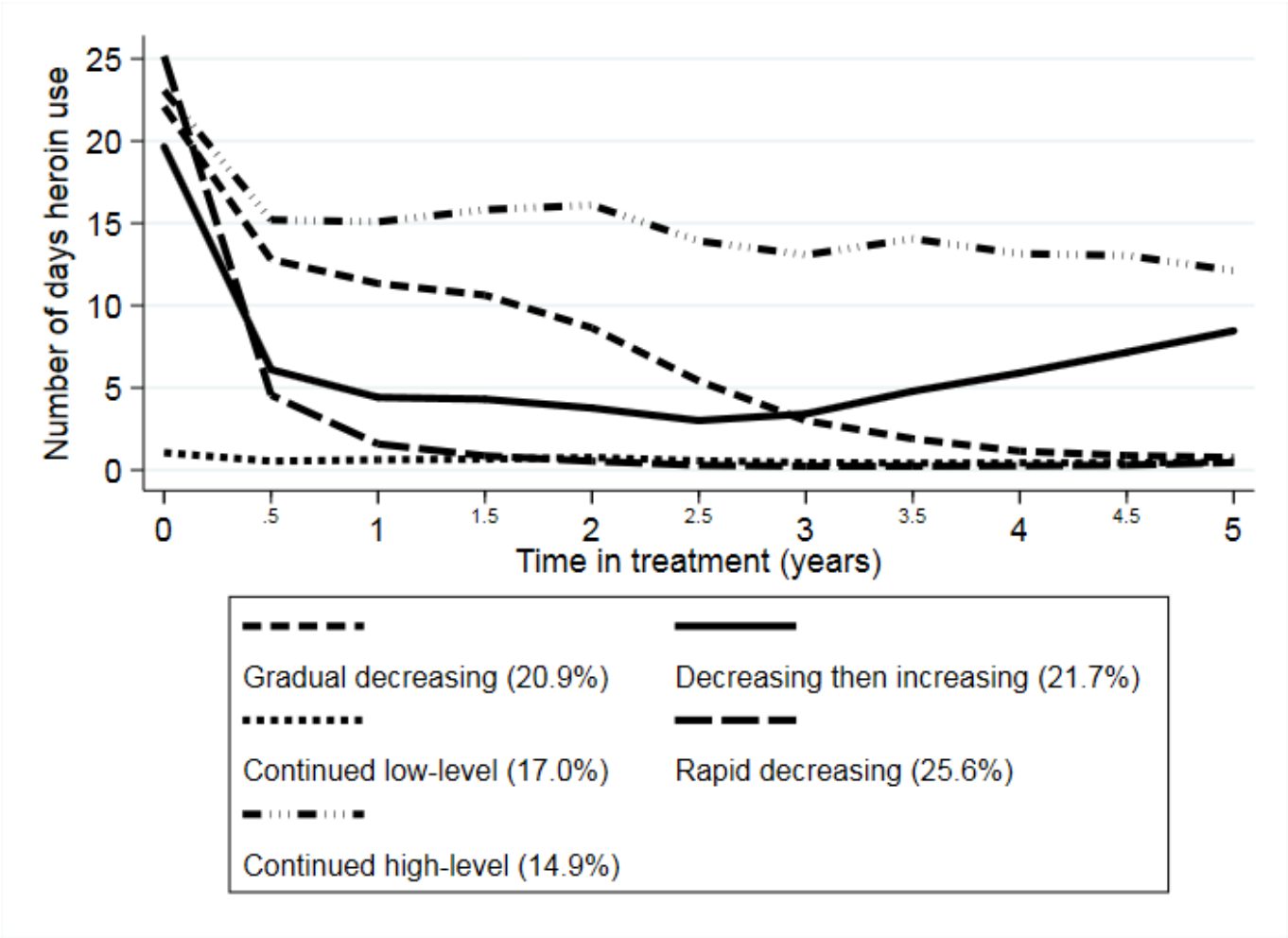
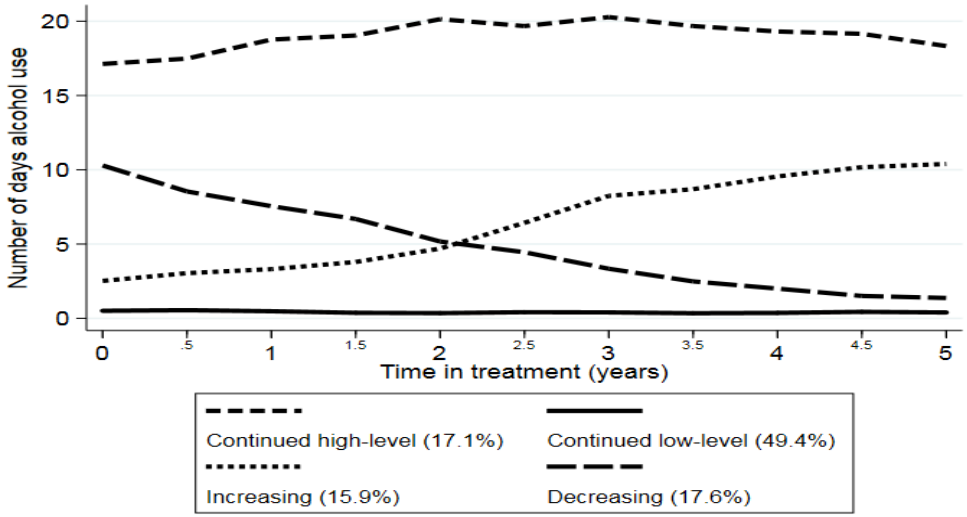
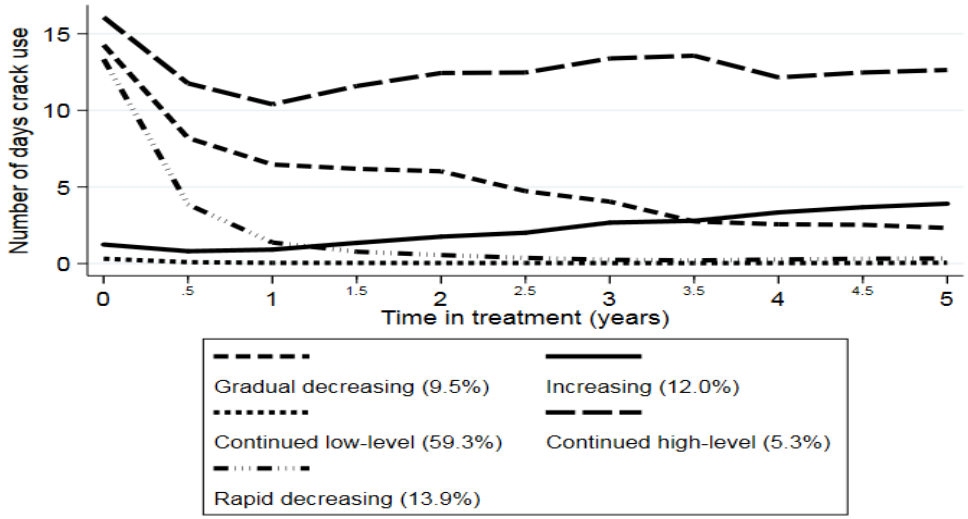


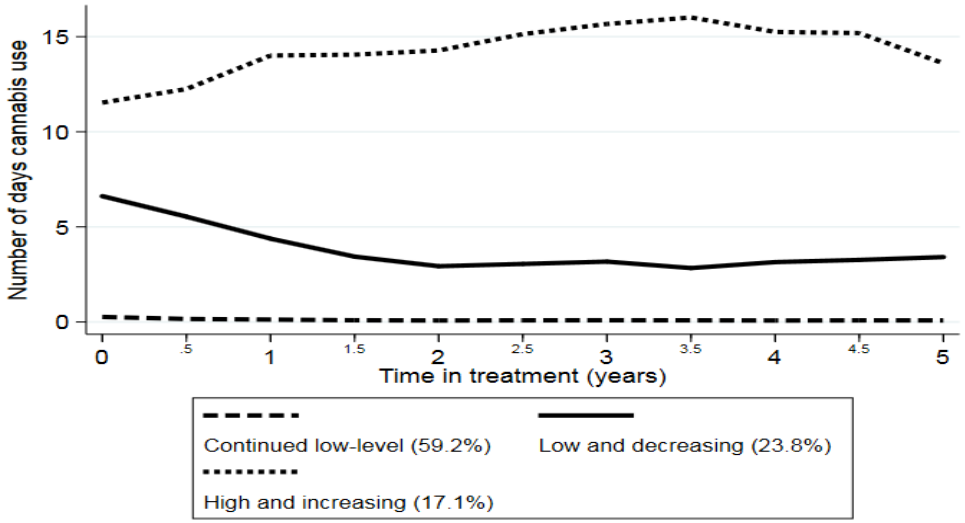
Figure 2. AOD trajectories over 5 years of continuous OST



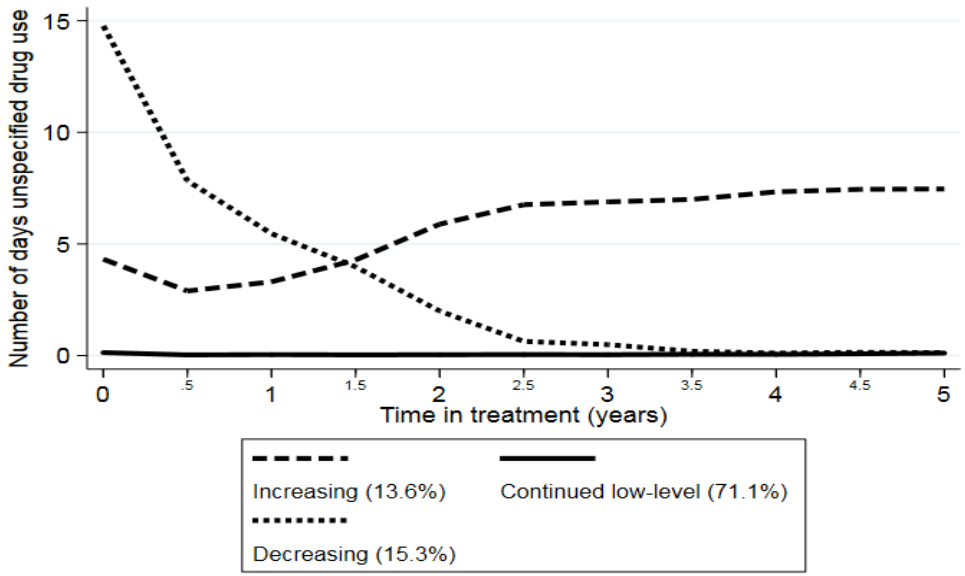
A. Alcohol use trajectories



B. Crack cocaine trajectories



C. Cannabis use trajectories



D. Unspecified drug use trajectories

References

Ali, R., Meena, S., Eastwood, B., Richards, I., Marsden, J., 2013. Ultra-rapid screening for substance-use disorders: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite). Drug Alcohol Depend. 132, 352–361. https://doi.org/10.1016/j.drugalcdep.2013.03.001

Benchimol, E.I., Smeeth, L., Guttmann, A., Harron, K., Moher, D., Petersen, I., Sørensen, H.T., Elm, E. von, Langan, S.M., Committee, R.W., 2015. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Med. 12, e1001885. https://doi.org/10.1371/journal.pmed.1001885

Borders, T.F., Booth, B.M., 2012. Stimulant use trajectories and the longitudinal risk of heavy drinking: Findings from a rural population-based study. Addict. Behav. 37, 269–272. https://doi.org/10.1016/j.addbeh.2011.11.003

Brecht, M.-L., Huang, D., Evans, E., Hser, Y.-I., 2008. Polydrug Use and Implications for Longitudinal Research: Ten-Year Trajectories for Heroin, Cocaine, and Methamphetamine Users. Drug Alcohol Depend. 96, 193–201. https://doi.org/10.1016/j.drugalcdep.2008.01.021

Budney, A.J., Bickel, W.K., Amass, L., 2002. Marijuana use and treatment outcome among opioid-dependent patients. Addiction 93, 493–503. https://doi.org/10.1046/j.1360-0443.1998.9344935.x

Castells, X., Kosten, T.R., Capellà, D., Vidal, X., Colom, J., Casas, M., 2009. Efficacy of Opiate Maintenance Therapy and Adjunctive Interventions for Opioid Dependence with Comorbid Cocaine Use Disorders: A Systematic Review and Meta-Analysis of Controlled Clinical Trials. Am. J. Drug Alcohol Abuse 35, 339–349. https://doi.org/10.1080/00952990903108215

Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017. Drug misuse and dependence: UK guidelines on clinical management. London: Department of Health.

Comiskey, C.M., Kelly, P., Leckey, Y., McCulloch, L., O'Duill, B., Stapleton, R.D., White, E., 2009. The ROSIE Study: Drug Treatment Outcomes in Ireland. The Stationery Office, Government Publications 978-1-4064-2278-8, Dublin.

Cornish, R., Macleod, J., Strang, J., Vickerman, P., Hickman, M., 2010. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ 341, c5475. https://doi.org/10.1136/bmj.c5475

Darke, S., Hall, W., 1995. Levels and correlates of polydrug use among heroin users and regular amphetamine users. Drug Alcohol Depend. 39, 231–235. https://doi.org/10.1016/0376-8716(95)01171-9

Darke, S., Slade, T., Ross, J., Marel, C., Mills, K.L., Tessson, M., 2015. Patterns and correlates of alcohol use amongst heroin users: 11-year follow-up of the Australian Treatment Outcome Study cohort. Addict. Behav. 50, 78–83. https://doi.org/10.1016/j.addbeh.2015.06.030

Darke, S., Williamson, A., Ross, J., Teesson, M., 2006. Reductions in heroin use are not associated with increases in other drug use: 2-year findings from the Australian Treatment Outcome Study. Drug Alcohol Depend. 84, 201–205. https://doi.org/10.1016/j.drugalcdep.2006.03.004

Department for Communities and Local Government, 2007. Index of Multiple Deprivation (IMD).

Eastwood, B., Strang, J., Marsden, J., 2018. Continuous opioid substitution treatment over five years: Heroin use trajectories and outcomes. Drug Alcohol Depend. 188, 200–208. https://doi.org/10.1016/j.drugalcdep.2018.03.052

Eastwood, B., Strang, J., Marsden, J., 2017. Effectiveness of treatment for opioid use disorder: A national, five-year, prospective, observational study in England. Drug Alcohol Depend. 176, 139–147. https://doi.org/10.1016/j.drugalcdep.2017.03.013

Epstein, D.H., Preston, K.L., 2003. Does Cannabis Use Predict Poor Outcome for Heroin-Dependent Patients on Maintenance Treatment? A Review of Past Findings, and More Evidence Against. Addict. Abingdon Engl. 98, 269–279.

Gossop, M., Marsden, J., Stewart, D., Kidd, T., 2003. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction 98, 291–303.

Gossop, M., Marsden, J., Stewart, D., Kidd, T., 2002a. Changes in use of crack cocaine after drug misuse treatment: 4–5 year follow-up results from the National Treatment Outcome Research Study (NTORS). Drug Alcohol Depend. 66, 21–28. https://doi.org/10.1016/S0376-8716(01)00178-8

Gossop, M., Marsden, J., Stewart, D., Kidd, T., 2002b. Changes in use of crack cocaine after drug misuse treatment: 4-5 year follow-up results from the National Treatment Outcome Research Study (NTORS). Drug Alcohol Depend. 66, 21–28.

Gossop, M., Stewart, D., Browne, N., Marsden, J., 2002c. Factors associated with abstinence, lapse or relapse to heroin use after residential treatment: protective effect of coping responses. Addiction 97, 1259–1267.

Grella, C.E., Lovinger, K., 2011. 30-Year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California. Drug Alcohol Depend. 118, 251–258. https://doi.org/10.1016/j.drugalcdep.2011.04.004

Heidebrecht, F., MacLeod, M.B., Dawkins, L., 2018. Predictors of heroin abstinence in opiate substitution therapy in heroin-only users and dual users of heroin and crack. Addict. Behav. 77, 210–216. https://doi.org/10.1016/j.addbeh.2017.10.013

Hubbard, R.L., Craddock, S.G., Anderson, J., 2003. Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). J. Subst. Abuse Treat. 25, 125–134. https://doi.org/10.1016/S0740-5472(03)00130-2

Marsden, J., Eastwood, B., Ali, R., Burkinshaw, P., Chohan, G., Copello, A., Burn, D., Kelleher, M., Mitcheson, L., Taylor, S., Wilson, N., Whiteley, C., Day, E., 2014. Development of the Addiction Dimensions for Assessment and Personalised Treatment (ADAPT). Drug Alcohol Depend. 139, 121–131. https://doi.org/10.1016/j.drugalcdep.2014.03.018

Marsden, J., Eastwood, B., Bradbury, C., Dale-Perera, A., Farrell, M., Hammond, P., Knight, J., Randhawa, K., Wright, C., 2009. Effectiveness of community treatments for heroin and crack cocaine addiction in England: a prospective, in-treatment cohort study. The Lancet 374, 1262–1270. https://doi.org/10.1016/S0140-6736(09)61420-3

Marsden, J., Eastwood, B., Jones, H., Bradbury, C., Hickman, M., Knight, J., Randhawa, K., White, M., the National Drug Treatment Monitoring System Outcomes Study Group, 2012. Risk adjustment of heroin treatment outcomes for comparative performance assessment in England. Addiction 107, 2161–2172. https://doi.org/10.1111/j.1360-0443.2012.03971.x

Marsden, J., Farrell, M., Bradbury, C., Dale-Perera, A., Eastwood, B., Roxburgh, M., Taylor, S., 2008. Development of the treatment outcomes profile. Addiction 103, 1450–1460. https://doi.org/10.1111/j.1360-0443.2008.02284.x

Marsden, J., Goetz, C., Meynen, T., Mitcheson, L., Stillwell, G., Eastwood, B., Strang, J., Grey, N., 2018. Memory-Focused Cognitive Therapy for Cocaine Use Disorder: Theory, Procedures and Preliminary Evidence From an External Pilot Randomised Controlled Trial. EBioMedicine 0. https://doi.org/10.1016/j.ebiom.2018.01.039

Marsden, J., Stillwell, G., Hellier, J., Brown, A.M., Byford, S., Kelleher, M., Kelly, J., Murphy, C., Shearer, J., Mitcheson, L., 2017. Effectiveness of adjunctive, personalised psychosocial intervention for non-response to opioid agonist treatment: Study protocol for a pragmatic randomised controlled trial. Contemp. Clin. Trials 53, 36–43. https://doi.org/10.1016/j.cct.2016.12.003

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev. CD002207. https://doi.org/10.1002/14651858.CD002207.pub4

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst. Rev. CD002209. https://doi.org/10.1002/14651858.CD002209.pub2

McLachlan, G., Peel, D., 2000. Finite Mixture Models. Wiley, New York.

McLellan, A.T., McKay, J.R., Forman, R., Cacciola, J., Kemp, J., 2005. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. Addiction 100, 447–458. https://doi.org/10.1111/j.1360-0443.2005.01012.x

Nolan, S., Klimas, J., Wood, E., 2016. Alcohol use in opioid agonist treatment. Addict. Sci. Clin. Pract. 11. https://doi.org/10.1186/s13722-016-0065-6

Public Health England, 2018a. Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2017 to 31 March 2018.

Public Health England, 2018b. Quality and Methodology Information. Public Health England, London.

Public Health England, 2017. Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2016 to 31 March 2017.

Public Health England, 2016. Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2015 to 31 March 2016.

Public Health England, 2015. Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2014 to 31 March 2015.

Russolillo, A., Moniruzzaman, A., McCandless, L.C., Patterson, M., Somers, J.M., 2018. Associations between methadone maintenance treatment and crime: a 17-year longitudinal cohort study of Canadian provincial offenders. Addiction 113, 656–667. https://doi.org/10.1111/add.14059

Sahker, E., Toussaint, M.N., Ramirez, M., Ali, S.R., Arndt, S., 2015. Evaluating racial disparity in referral source and successful completion of substance abuse treatment. Addict. Behav. 48, 25–29. https://doi.org/10.1016/j.addbeh.2015.04.006

Scavone, J.L., Sterling, R.C., Van Bockstaele, E.J., 2013. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience 248, 637–654. https://doi.org/10.1016/j.neuroscience.2013.04.034

Sifaneck, S.J., Kaplan, C.D., 1995. Keeping Off, Stepping on and Stepping Off: The Steppingstone Theory Reevaluated in the Context of the Dutch Cannabis Experience. Contemp. Drug Probl. 22, 483–512.

Simpson, D.D., Joe, G.W., 1993. Motivation as a predictor of early dropout from drug abuse treatment. Psychother. Theory Res. Pract. Train. 30, 357–368. https://doi.org/10.1037/0033-3204.30.2.357

Simpson, D.D., Joe, G.W., Bracy, S.A., 1982. Six-year follow-up of opioid addicts after admission to treatment. Arch. Gen. Psychiatry 39, 1318–1323.

Simpson, D.D., Joe, G.W., Rowan-Szal, G., Greener, J., 1995. Client engagement and change during drug abuse treatment. J. Subst. Abuse 7, 117–134. https://doi.org/10.1016/0899-3289(95)90309-7

Stahler, G.J., Mennis, J., DuCette, J.P., 2016. Residential and outpatient treatment completion for substance use disorders in the U.S.: Moderation analysis by demographics and drug of choice. Addict. Behav. 58, 129–135. https://doi.org/10.1016/j.addbeh.2016.02.030

Teesson, M., Marel, C., Darke, S., Ross, J., Slade, T., Burns, L., Lynskey, M., Memedovic, S., White, J., Mills, K.L., 2017. Trajectories of heroin use: 10–11-year findings from the Australian Treatment Outcome Study. Addiction 112, 1056–1068. https://doi.org/10.1111/add.13747

Teesson, M., Ross, J., Darke, S., Lynskey, M., Ali, R., Ritter, A., Cooke, R., 2006. One year outcomes for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Drug Alcohol Depend. 83, 174–180. https://doi.org/10.1016/j.drugalcdep.2005.11.009

Valdez, A., Cepeda, A., Neaigus, A., Russell, A., 2008. Heroin transition risk among daily and non-daily cannabis users who are non-injectors of heroin. Int. J. Drug Policy 19, 442–449. https://doi.org/10.1016/j.drugpo.2007.06.004

Weiss, R.D., Potter, J.S., Griffin, M.L., Provost, S.E., Fitzmaurice, G.M., McDermott, K.A., Srisarajivakul, E.N., Dodd, D.R., Dreifuss, J.A., McHugh, R.K., Carroll, K.M., 2015. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug Alcohol Depend. 150, 112–119. https://doi.org/10.1016/j.drugalcdep.2015.02.030

White, M., Burton, R., Darke, S., Eastwood, B., Knight, J., Millar, T., Musto, V., Marsden, J., 2015. Fatal opioid poisoning: a counterfactual model to estimate the preventive effect of treatment for opioid use disorder in England. Addict. Abingdon Engl. 110, 1321–1329. https://doi.org/10.1111/add.12971

Willey, H., Eastwood, B., Gee, I.L., Marsden, J., 2016. Is treatment for alcohol use disorder associated with reductions in criminal offending? A national data linkage cohort study in England. Drug Alcohol Depend. 161, 67–76. https://doi.org/10.1016/j.drugalcdep.2016.01.020

Zarkin, G.A., Dunlap, L.J., Hicks, K.A., Mamo, D., 2005. Benefits and costs of methadone treatment: results from a lifetime simulation model. Health Econ. 14, 1133–1150. https://doi.org/10.1002/hec.999